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Dockets Management Branch (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2003D-0367; Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions; Draft Guidance; 68 Federal Register 52044

Dear Sir/Madam:

The following comments on the above draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2002, our members invested over $32 billion in the discovery and development of new medicines.

PhRMA supports FDA's desire to utilize common technologies for electronic submissions that are consistent with the ICH electronic Common Technical Document (eCTD).

Guidance consistency across review divisions is effective for sponsors. PhRMA also recommends that the Center for Devices and Radiologic Health also consider adopting this guidance.

It would be beneficial to provide a mapping from the CFR requirements, specifically for IND and for IND and NDA annual reports, to the new modular structure, specifically to Module 1. It is not always clear how to provide information described in the CFR within the Module 1–5 structures.

The following comments apply across all documents:

- Title and Line 57: As the guidance applies to submissions to both CDER and CBER, 'Biologics' or 'Biopharmaceutical' products need to be mentioned along with 'Pharmaceutical' products.
- The requirements for granularity and hypertext linking are extremely specific. It is, therefore, of utmost importance that there is harmonization between the three key regions.
- Top-level tables of contents (TOCs) are specified for most sections. However, the ICH eCTD deliberately omits such TOCs, because the backbone provides navigation.
- It would be beneficial for FDA to comment on archive mechanisms for submissions provided via the eCTD specification.

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I. Introduction
On lines 32-33 the statement suggests this specific guidance will cover harmonization between submission type; however, on lines 72-73, the document indicates harmonization will be covered in separate guidance documents. This should be reconciled or clarified.

On lines 35-36 and throughout the document (lines 119-122, line 129, lines 172-173, lines 596-597, and line 693) there are references to the "*Regulatory Submissions in Electronic Format — General Considerations*" guidance. Even the revision that was published on October 21, 2003 contains information that is no longer relevant. For example, it still refers to a physical media standard of CD-ROM using the ISO-9660 standard that cannot accommodate the long files, the lower case character file names, or the dash that is used in the eCTD.

II. D. Document Granularity and Table of Contents Headings
On line 91 it says, "When making an electronic submission, each document should be provided as a separate file." Industry will need to define what is considered a "document" and what can be combined into a "document". Documents that are very large will need a process for where to divide the document into separate files to meet this requirement.

On line 98, it is not clear whether this is referring to the inclusion of a physical submission-level TOC in the application. The eCTD specification omits a physical TOC (i.e., no CTD sections 2.1, 3.2, 4.1 or 5.1), because it is intended that the XML backbone provides contents and navigation for the submission. This should be clarified.

Footnote 3 is vague and meaningless. If this footnote is needed, the phrase "too large" should be quantified.

Line 108-109: The meeting background material may contain information on different aspects of the drug development process namely quality, nonclinical, and clinical as well as summaries. Should they all be combined together in one document as the Meeting Background Material or placed in the appropriate modules (1-5)? Additional guidance on the organization of background material will be helpful.

Line 111-112: Additional guidance is necessary for the following scenario:
When a file (with unique ID) is associated with multiple headings in a submission and the document associated with only one particular heading needs to be deleted or altered (using the Operation attribute), the deletion or alteration will likely affect the document associated with all other headings. How should the situation be handled?

II. E. Electronic Submissions
Line 122-123 states, "These guidances do not recommend using the eCTD backbone files described in this guidance. However, PhRMA recommends begin submitting eCTD backbone files described in this guidance because...". This could cause potential conflicts as one set of guidance [Providing Regulatory Submissions in Electronic Format-NDA, Providing Regulatory Submission in Electronic Format-ANDA, and Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format-Biologics Marketing Applications] does not recommend using the eCTD backbone and yet this guidance document does. Which guidance will industry need to follow and what will the FDA expect to see?

Line140-142: How far in advance can the sponsor obtain an application number? What happens if the submission is indefinitely postponed or cancelled? Does the FDA have to be notified?

II. G. Referencing Previously Submitted Documents

Although lines 155 and 156 indicate that the sponsor would not have to provide eCTD backbone files for previous submissions to the application, lines 163-165 appear to conflict with that statement indicating that, when referencing a previously submitted document, the sponsor would not have to submit additional copies, providing the document was submitted in electronic format with the proper electronic document information included in the eCTD backbone files.

On line 163 the guidance does not provide sufficient detail on how sponsors should reference previously submitted information. This section should be enhanced.

Further, additional guidance is needed to describe how to provide reference to information not generated by the sponsor, e.g., where a sponsor is responding to agency-requested information and there is a need to reference the specifics of the request.

It would be helpful, additionally, if FDA could provide information on how the Agency's eCTD Viewer System (EVS) will allow for navigation among disparate applications and their many files, so that sponsors can adequately supply appropriate navigational links.

In lines 176–179, in the case of providing an electronic copy of the previously submitted paper documents, what is the correct operation attribute: 'new' or 'replace'. If the sponsor is submitting an electronic copy of the previously submitted paper document, is there still a need to submit the cross-reference information outlined in lines 173-175?

In lines 181–182: please provide clarification on how a sponsor can refer to another application based on the current ICH eCTD specification.

II. H. Refuse to File

In line 184 it says "We may refuse to file an application or supplement under our regulations (e.g. 314.101 and 601.2) if the submission is illegible, uninterpretable, or otherwise clearly inadequate including having incompatible formats or inadequate organization." What will the process be if the submission does not comply with the technical requirements or is considered uninterpretable? Will there be an error-reporting feature to enable the submitter to fix the XML and resubmit the document again?

In lines 189-190, the draft guidance states, "The absence of electronic datasets in an acceptable format to permit review and analysis may be considered inadequate, resulting in a refuse to file decision". The definition of "acceptable format" should be clarified or the predicate rules should be mentioned.

II. I. Submission of Paper Copies

In lines 197-198, FDA has identified the proliferation of disparate versions of electronic and paper files, often due to requests for desk copies. PhRMA believes this statement could be strengthened for clarity, i.e., by replacing the final phrase with 'are not required' rather than 'are not needed'. Guidance is needed to describe the procedures that sponsors should follow if such copies are requested by the Agency.

II. J. Scanned Documents

In line 200 it says "Scanned documents submitted electronically as images are not as useful for review as documents that are text based." And line 205 states "For these reasons, we strongly urge that you provide text-based documents, rather than image files, whenever possible. And line 209 states "However, we expect documents such as study reports recently generated by the company or recently generated as the result of the company's request to be available as text-based documents." This could have a big impact as many casebooks (CRF pages) are still hard copy pages that are currently being scanned and submitted as images. How will this affect the CRF case book process?

Lines 211-214 state "We understand that legacy study reports, those generated years ago, may only be available in paper. For these reports, especially those for pivotal studies, you may want to consider converting these documents from image files to text-based files using optical character recognition (OCR) or some other technique." This could be costly and would require validation of new software to do the OCR process. How does industry determine which legacy documents to convert and which ones do not need to be converted? OCR will probably require manual rework of documents. It would be valuable to document Agency expectations surrounding scanned (image-based) documents. Any additional details that will clarify the Agency's position on scanned documents would be beneficial, so sponsors can best respond to reviewer needs.

II. K. The Field Copy

Lines 218-219 say that separate field copies do not have to be provided. It is assumed that a separate letter to the district office referencing the submission is still appropriate. Should this letter contain particular electronic identification numbers for ease of retrieval for the field? What mechanism will be used to alert the district offices that a field copy is available? Will the terminology on the field certification need to be changed?

II. L. Electronic Signatures

The draft Guidance is unclear regarding both the requirement (and preference) for, and the mechanism for submission of, electronic signatures. The use of the word 'can' as opposed to 'should' in line 224 infers that electronic signatures are not required, though statements by Agency personnel at the Aug 28 DIA/FDA meeting suggest that electronic signatures are required for electronic submissions. The proviso that the Agency's system can automatically validate the signature requires clarification (i.e., how do sponsors know what the Agency's system can automatically validate?).

II. M. Number of Copies of Electronic Files

Lines 230-231 say sponsors "should not send copies directly to the reviewer or review division", but follows with the instruction "without following procedures described in this Guidance". As there are no specific instructions contained in the Guidance regarding the mechanism for

providing copies to the reviewer or review division, the following wording is recommended to eliminate any ambiguity:

> "Provide only a single copy of the electronic portions of a submission to the appropriate central document room facility as described in Section R of this document. Copies should not be sent directly to the reviewer or review division. Do not bypass the controls for electronic files described in 21CFR 11, as doing so would make the documents unreliable for review."

Please provide information on what kind of color jackets should be used for submitting the electronic media, e.g. blue for NDAs and sNDAs, red for INDs.

II. N. Naming Electronic Files
Line 240-241: Will the FDA prefer the files to be named as per the ICH eCTD specifications version 3.0 (e.g., Analytical Method –1, Analytical Method –2 etc.) or should all filenames be indicative of the content? Specific guidance will be appreciated.

II. O. Naming folders
On lines 244-253 it would be valuable to state that (blank) spaces are not allowable in naming folders.

On lines 247-250 and line 324 what is the difference between a "main sequence folder" and a "main submission folder"? If they are the same, it is recommended that the terminology be used consistently throughout the Guidance.

On line 251, PhRMA suggests "64 digits" be changed to "64 characters".

II. P. File Formats
In line 264, it indicates "SAS XPORT transport files (.XPT) for dataset" are needed. It should be noted that XPORT transport files are Version 5.

In line 270, please clarify the statement "(check our Web site for the current version)", including the rationale behind this. Please provide the link to the website.

On line 265, it says "ASCII text files or SAS files for statistical program controls (e.g., SAS program files, NONMEM control files) using txt for the file extension". It should be clarified that SAS program files are ASCII files.

II. Q. PDF Bookmarks and Hypertext Links
In line 284, remove the word "for".

II. R. Sending Electronic Submissions:
On lines 310-311, e-mail is proposed as an appropriate way to transfer submissions of less that 50 megabytes in size. PhRMA does not consider e-mail as a reliable way to transfer regulatory information, archive this regulatory activity, track these electronic submissions or provide the adequate safeguards if there is a transmission failure. E-mail systems are also not compliant with 21 CFR Part 11. Companies are already building systems for transmission and receipt of

electronic submissions using FDA's gateway. PhRMA proposes utilization of FDA's gateway for this purpose.

III. Organizing the Main Submission Folder

On line 322 it would be useful to reference additional guidance documents, as referenced in Section 1, specifically for the various subsections of Section III.

On line 324-333, it is unclear when the numbering would start. Since the guidance addresses the IND and the NDA/BLA, would the numbering start with the first submission in the IND and continue sequentially through the NDA?

III. A. *2.* Cover letter (optional)

If a cover letter is not provided, where should we place the information that is listed in lines 364-370?

III. A. 3.Labeling

On line 372, please provide guidance on how to handle 'CBEs'. How can 'current labeling' be submitted?

On line 398, the proposed new labeling format requires columns; however, this guidance specifies no columns. This discrepancy should be rectified.

On the same page, footnote 6 is not clear, and reads as if incomplete.

III. A. *5.* Marketing annual reports

When does the eCTD Annual Report take precedence over public docket 2003D-0364 of August 28, 2003 (FR 68 51788 Draft guidance... Regulatory Submissions in Electronic Format-Annual Reports for NDAs and ANDAs)? The August 2003 Guidance for NDAs and ANDAs uses the eNDA structure. Will this be withdrawn or updated in accordance with the final FDA eCTD submission requirements/guidance?

This section covers NDA Annual Reports. Will additional guidance be offered for IND Annual Reports?

In line 452, how would the situation be handled when a single Annual Report is used to report all NDAs for a product and some were eCTD submissions and some were paper?

In line 461, please provide your expectations as well as examples with regards to the type of information to be included under Safety Information in Marketing Annual Reports.

In line 462, it appears that "labeling changes" (under marketed annual reports) is a subset of "labeling history" (see line 376). Please clarify the Agency's expectations with regard to the content of these two sections.

On line 467, because the "CMC Changes" file for NDA Annual reports would be included in Module 1, please clarify circumstances for information to be placed in Module 3.

Lines 472-474 indicate that a bookmark should be provided for each study described in the "postmarketing study commitments "and "status of other postmarketing studies". Please indicate whether hypertext links/bookmarks from other sections of the Annual Report, e.g., "Appropriate Nonclinical Studies", "Clinical Pharmacology information" to referenced Study Reports should be included.

III. A. 6. IND annual report

PhRMA understands that all parts of the IND Annual Report will be included in Module 1 and most for the NDA Annual Report (with the exception of associated study reports, which will be located in Modules 4 and 5, as indicated). Please provide clarity to the Headings and Hierarchy document. It is not necessarily easy to discern to which the headings apply – some may apply to both; however, most would appear to apply to NDA Annual Reports only. Some examples of specific contributions to the IND Annual report (per CFR) are currently unlisted: Significant Phase 1 Protocol Modifications; Investigator's Brochure (indicating changes since the last edition); Significant Foreign Marketing Developments (the listed document on the Headings and Hierarchy document is Foreign Marketing History).

III. A. *7.* Information amendments

In line 491-492, what type of information would you expect to see in Module 1 for information amendments related to safety, efficacy etc.? Additional or modified information would be included in the appropriate modules.

In lines 494-495, please provide an example of an Information Amendment that is not relevant to Modules 2-5 or any other CTD heading?

In lines 496-497, please clarify what is meant by "Multiple Module Information Amendments".

III. B. Module-2 Summary folder

Will the Agency provide guidance on how to utilize the headings/subheadings in Module 2 for INDs, DMFs, amendments etc. (submissions other than original NDAs ANDAs)? Supplying information under each of the headings in the summary module would not be necessary for a simple IND amendment or perhaps even for a Phase I IND. Should the headings all appear in the submission with "NA" beneath?

In line 501-503, the draft guidance says, "The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the example provided with this document." It is assumed that the example referenced is the Draft, Comprehensive Table of Contents – Headings and Hierarchy document. Please clarify.

Further clarification is needed regarding how to meet the granularity since the headings in the Draft Comprehensive Table of Contents – Headings and Hierarchy (Draft TOC) do not seem to match the nodes available within the eCTD DTD. The Draft TOC document suggests the following content files for the QOS in the following order (see page 7 of this document), "General Information", "Manufacturer", "Characterization", "Control of Drug Substance", "Container Closure System", "Stability", "Description and Composition of the Drug Product", "Pharmaceutical Development", "Manufacturer", "Control of Excipients", "Control of Drug Product", etc. The ICH eCTD DTD supports only the following nodes: "Introduction", "Drug Product", "Drug Substance", "Appendices", and "Regional Information". It will be possible for

sponsors to attach multiple leafs to these nodes and provide the level of granularity suggested by the Draft TOC; however, further specific guidance should be provided regarding this requirement.

FDA should provide guidance for naming files and leaf title information if it is requiring a level of granularity different from that suggested by the ICH eCTD DTD.

III. C. Module-3 Quality folder

On lines 511-516, it indicates that sponsors should follow the level of granularity at the lowest level of the hierarchy defined in the Draft Comprehensive Table of Content – Headings and Hierarchy (Draft TOC). Further clarification is needed regarding the requirements for Module 3 based on the Draft TOC.

Page 10 of the Draft TOC does not show a hierarchy suggesting that the "Components of the Drug Product & sub-sections" and the "Drug Product & sub-sections" are both detailed sub-sections of the "Pharmaceutical Development" section. Additionally, further guidance should be given specifying the use of standard title information to clearly identify the sub-sections of Pharmaceutical Development should a sponsor decide to submit each sub-section as a separate file since the eCTD DTD does not provide separate nodes for this level of granularity.

Page 12 of the Draft TOC indicates that 3 sub-sections of the Regional information will be possible. Further guidance should be provided regarding the use of standard title information to clearly identify the various files that would reside in these sub-sections since the eCTD DTD does not provide nodes for these sub-sections.

In line 522, additional guidance regarding what the Agency considers to be a "short and meaningful" filename is requested.

III. D. 1. Study reports

On lines 539-565 the ICH eCTD specification suggests that a multiple-files report is relevant only if the report is very large. PhRMA believes multiple files should be avoided if possible. FDA should clarify this point.

On lines 559-565, PhRMA is not aware that ICH has defined the sectional breakdown for a preclinical study report. It would be beneficial to agree to such a breakdown as part of ICH. Such an agreement would eliminate a situation where different authorities could require a sponsor to submit the same content in different files, which would be an unnecessary burden.

On line 542, the 'Legacy Study Report' is not relevant. That should be the default for this type of report, because 'typically, a single document should be provided.

Review of the study report breakdown suggests that the list may need a number of editorial changes, e.g., line 546 would typically read 'Signatures of study director'; line 553 'compliance' may not be relevant; line 554 'individual' should be 'animals', etc.

On lines 554-565 and 553-565, because of the use of bullets and indented dashes, it is not clear whether the list is intended to convey that data tabulations, data listings, analysis datasets, and IND safety reports (along with the tabulations, definitions and programs listed for

each) should be submitted as a single document (Individual subject data listings), or whether each of these items should be a separate document.

On lines 569-571 and 619-621, is it necessary to resubmit a document electronically if it had been previously submitted in paper, or does the simple reference mentioned include reference to a paper submission?

On line 570, in order to ensure consistency for sponsor requirements, agreement on whether to include a preclinical protocol with a report, rather than as a separate file, should be agreed at ICH.

On line 572 it may be necessary to clarify how FDA would interpret a study director's statement and applicability of the signature as it relates to additional files that might be delivered later. Would an additional signature be needed?

On lines 576-578 the guidance would be strengthened if a different, less obvious, example is used.

In lines 580-581, it states "When providing a study report in more than one document, you should include the Study Tagging File (STF) described in the attachment Study Tagging File Specification". We believe a Study Tagging File should be required for every report, regardless of whether it is in a single file or in multiple files, because the STF includes valuable information, such as route of administration and species information.

The draft guidance also implies that sponsors should organize their eCTD table of contents similar to that specified in the Draft Table of Contents – Headings and Hierarchy (Draft TOC).

- Further guidance is needed regarding how to organize the eCTD and use the title fields if a STF file is not needed since the draft guidance indicates that the STF is only necessary when submitting more than one file related to a study;
- Further guidance is needed regarding how to provide dose information for Single Dose Toxicity studies since the Draft TOC indicates that Dose should be provided (see page 14), and
- Further guidance is needed regarding how to provide duration information for Repeat Dose Toxicity studies since the Draft TOC indicates that Duration should be provided (see page14)

III. D. 3. Datasets

On line 588-593 the location specified for datasets is not consistent with the ICH eCTD specification. While these datasets are currently required only by FDA, the Agency should request a change to the specification at ICH if this guidance is to remain as written.

It would be valuable if FDA included a representative structure for the datasets placement.

In lines 590-593, it describes how to organize the preclinical datasets. However, there are no corresponding tags identified for the datasets or related files in the Attachment "The eCTD Document Information Backbone Files Specification for Modules 2 through 5".

In line 592-593 and Line 687-688, please clarify the use of datasets folder. Should all files for a study – text and data – be in the datasets folders or are there two locations of study data in the file directory?

III. E. Module-5: Clinical Study Reports folder

In line 600, the name for this section is different from the name listed in the "Comprehensive Table of Contents Headings and Hierarchy" and "Attachment The eCTD Guidance Information Backbone Files Specification for Modules 2 through 5" documents where it is just listed as "Efficacy".

On lines 603-607, it says, "The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the attachment on Table of Contents Headings and Hierarchy provided with this guidance." It goes on to say that, "Each document should be provided as an individual PDF file." Further guidance is needed regarding "Antibacterial Reports" and "Antiviral Reports" and how to specify the related PDF content files within a STF.

III. E. 2. Study reports

In line 616, please clarify whether the Agency specifically wants any, or each, of the bulleted items to be provided as individual documents.

Does the Agency desire that all sponsors take a standard approach to providing these elements as individual documents?

Please clarify whether the interim analysis plan can (or should) be submitted as a separate document from the statistical methods, or whether these can be combined.

Footnote 8 states, "When providing a study report in more than one document, you should include the Study Tagging File (STF) described in the attachment Study Tagging File Specification." We believe that a Study Tagging File should be required for every report, regardless of whether it is in a single file or in multiple files, because the STF includes valuable information that will aid in navigation and information retrieval.

On line 626 and the corresponding footnote 9, this should be broken out separately from the list.

On line 630, "Protocol amendment [number] (E3 16.1.2)" should be (E3 16.1.1) according to E3.

On lines 654-663, a clear definition of "data tabulation", "data listing" and "analysis data set" should be provided. There is also no mention of the Blank Annotated CRF. It is assumed that this would be included as a part of the various Data Definitions (i.e., lines 656, 659 or 663) or immediately following these files. Please confirm.

On line 666 it should be possible to define additional appendices beyond the E3 specified appendices. Companies report that they typically include appendices such as: bioanalytical results; certificates of analysis; pharmacokinetic or population pharmacokinetic report;

biomarker report; pharmacogenetic results; health outcome report on direct cost data; virology genotypic and phenotypic results, etc. These do not fit into the classifications specified.

III. E. 3.Case report forms
On line 669, it says, "You should provide each individual subject's complete CRF as a single PDF file." The definition of "each individual subject's" CRF should be clarified or the predicate rules should be mentioned since CRFs are only required by regulation for subjects that have died and/or discontinued due to Adverse Events.

On lines 672-674, it says "If electronic data capture was used in the clinical trial, you should submit a PDF-generated form or other PDF representation of the information." "Other PDF representation" is too ambiguous and should be defined or clarified.

On line 676, it states, "You should use the subject's unique identifier as the title of the document and the file name. These names are used to assist reviewers in finding the CRF for an individual subject." While the use of the title attribute within the leaf should be clarified, it does not seem like the best mechanism for specifying patient ID for patient CRFs, patient profiles or, in the future, for ECG waveform files. This information should be placed into a more structured location specifically defined for patient ID values. The "property" element within the file tagging structure would seem to be a more logical place to hold this information (similar to what has been defined for "site-identifier"). Additionally, this would allow the sponsor to use the title field to offer brief descriptive text explaining unique situations such as the submission of an incomplete patient case followed by a "final / complete case" or the submission of an addendum, etc. An example using the property could look like the following:

<property name = "patient-identifier" info-type = "fda">1234</property>

NOTE: there is no mention of title field nomenclature for the submission of patient profiles or other related patient information such as patient wave form data within this section of the draft guidance.

III. E. 4.Datasets
On line 686 there is another deviation from the ICH eCTD Specification. FDA should propose this model for ratification at ICH, which would then trigger a specification update.

III. E. 5. Periodic safety update reports
In lines 696-709, within the DTD, there is no organization of the periodic safety updates. Please provide additional clarification.

In lines 696-709, please confirm that if a sponsor is still doing ICSRs in paper, the descriptive information should also be in paper.

IV. B. Style and PDF Index Folder
Change the title of this section to just "Style" since PDF index folders are not addressed.

On line 729, it says "You should use the most recent stylesheet." The "most recent stylesheet" should be enhanced to make it more useful. Some of the needed enhancements are listed below:

- Does NOT provide a display per ICH CTD specifications or per the FDA draft specification Table of Contents.
- Does not allow collapsing/expanding by sections/sub-sections
- Does not provide visual queues (e.g. indentation) to indicate the CTD hierarchy.
- Does not display attributes for repeating nodes in all cases. For example, in M3:
  1) Does not display attributes for repeating m.3.2.s (substance, manufacturer);
  2) Does not display attributes for repeating m.3.2.p (product name, manufacturer, dosage form);
  3) Does not display attributes for repeating m.3.2.p.4 (excipient).
  4) In Module 5, it does not display attribute for repeating m.5.3.5 sections (indication)
- Does not display multiple node extensions.
- Does not provide a visual queue to track that someone is within a section after they have scrolled down beyond the section header (nice to have something similar to what is done within the STF style sheet where a line is drawn on the left-hand side as a visual queue that the viewer is within a particular section).
- It would be valuable to have a visual queue indicating the operation value displayed on the line with the title (although this is a single instance viewer, it would be beneficial to identify the operation associated with each file)

Note that the ICH eCTD Specification (Page 1-1) indicates that, "A standard stylesheet for viewing the eCTD submission is defined and provided by the ICH M2 EWG."

Comprehensive Table of Contents Headings and Hierarchy

The specification identifies the topmost (first) node for sections M2, M3, M4 and M5 as a Table of Contents entry. While it is technically feasible to place a TOC at these locations, it is not compliant with ICH specification.

It would be extremely helpful if a mapping was provided to the corresponding CFR entry and having a version numbering or dates associated with the Comprehensive Table of Contents Headings and Hierarchy would be helpful.

For eINDs, several IND items are not listed in the Comprehensive Table of Contents whereas others are. PhRMA was hoping for a complete list of where to put all IND documents.

Please confirm that the bolded items listed are expected designated headers in the Module TOCs, e.g., in the m1 TOC, Forms would be designated in the TOC. Would this also be a folder (e.g., Forms)?

On page 2 there is an item named "Field Copy Certification". Why is this item included when the field copy is not needed (see line 216 in the main guidance document)?

On page 4, what are examples that might appear in the section named "Quality information amendment"?

On page 7, for M2 Summaries, there appears to be a missing reference to Introduction for the Quality Overall Summary.

On page 7, please adjust the hierarchy of the outline to correctly coincide with the CTD. Under the heading "Pharmaceutical Development", demote "Drug Substance", "Excipients", "Formulation Development", "Overages", and Physicochemical and Biological Properties".

On page 9, the Drug Substance [name, manufacturer] is a node structure where it is being represented by the FDA Table of Contents. The attributes name and manufacturer can be applied at this point, but there is no heading to update with these data. Under this model, the Agency's EVS will have to manage this as part of the rendering process. The same situation will exist for the Drug Product specification on page 10.

On page 12, rather than place a breakdown under a primary pharmacodynamics study, which normally would not contain the elements listed, it would be better to use a toxicology study as an example. Also, the section numbers (E3) are inappropriate for a preclinical study.

On pages 13-16, reference is repeatedly made to 4.2.1.1; however, this guidance is not numbered. Are these references to the CTD Safety document?

On page 13, under analytical methods and validation reports, the reference to 4.2.1.1 is tenuous, because this type of report would not contain such data.

On page 16, the Module 5 title in this document is "Module 5 Efficacy" and in the main guidance document it is "Module-5: Clinical Study Reports" (see line 600). In the "Attachment The eCTD Document Information Backbone Files Specification for Modules 2 Through 5" document the title is "Module 5:Efficacy.

On page 16 it is unlikely that a bioavailability study would contain all of the E3 appendices. This example would better fit in one of the efficacy sections.

On page 19, indication is an attribute at this point; however, you cannot update the heading to represent indication. The attribute will need to be updated and the rendering tool will need to accommodate this.

On page 22, in the CRF section, CTD section 5.3.7 is missing. If this is to indicate the expectation that CRFs will be filed with the study report, then it amends the CTD specification, and is not consistent with the current eCTD specification as issued under ICH.

Attachment The eCTD Document Information Backbone Files Specification for Modules 1
It would be beneficial to recommend file names for Module 1 documents.

It would be beneficial to provide a mapping from the CFR requirements, specifically for IND and for IND and NDA annual reports, to the new modular structure, specifically to Module 1. It is not always clear how to provide information described in the CFR within the Module 1–5 structure.

On page 1, paragraph 1; we suggest changing "This discusses" to "This guidance discusses".

On page 1, paragraph 2, we suggest changing "...eCTD backbone files are organize..." to "...eCTD backbone files are organized...".

On page 1, paragraph 4, we suggest changing "...submission type..." to "...submission types...".

On page 1, paragraph 4, we suggest changing "The remainder of this document provide..." to "The remainder of this document provides...".

On pages 1, 2, and 7, we suggest changing "Guidance to Industry" to "Guidance for Industry" to agree with the actual titles of the guidance documents cited.

On page 5 PhRMA suggests adding new attribute names and values for "safety-supplement" and "promotional-material".

On page 6, what are the 3 asterisks referring to after "Related-sequence-number"?

On page 6, in the non-XML representation, Sequence-number 0006 should be related to sequence number "0003", not "0000".

On the second line of page 7, change "<sequence-number>0006</sequence-number>" to "<sequence-number>0007</sequence-number>".

On page 7, section III. B., in the last sentence of the first paragraph, change "...14 XML heading..." to "...16 XML heading...".

On page 9, the tags suggest a single letter of authorization. How would we submit several letters of authorization (e.g., from several suppliers)?

On page 9, should "Letter of Authorization" be changed to "Letters of Authorization"?

On page 9, entry 4. c, change "List of Authorized to Persons..." to "List of Authorized Persons...".

On page 16, section IV, paragraph 1, line 3 should be phrased differently. For example, Form 356h and 3397 can occur together in one submission.

On page 31, "INFORMATION ADMENDMENT" should be changed to "INFORMATION AMENDMENT".

Attachment The eCTD Document Information Backbone Files Specification for Modules 2 through 5

It would be very helpful to have version numbering or dates associated with this document.

I. START AND FINISH OF THE MODULE 2 TO 5 ECTD BACKBONE FILE
Line 48 has a foot note number 15, which seems to make no sense.

II. A. *leaf* element table
On row 9 of the table, it would be better to provide an example for a relative path of a document in Module 2 – 5.

II. C. *leaf* element detail
On line 163 there is another deviation from the ICH eCTD Specification. The leaf ID is currently optional in the ICH eCTD Specification. FDA should raise the leaf ID as mandatory rather than deviating from the harmonized document.

On lines 190-194, the *modified-file* attribute is described, however, the content of this attribute differs from the ICH eCTD Step 5 Specification document. Instead of providing the relative file name of the file you are modifying, we are to provide the file name of the backbone for the submission containing the file you are replacing along with the ID value of the leaf ID for that file. This should be agreed at ICH before adoption at a regional level. In the following example, FDA wants the "modified-file" attribute completed as follows:

modified-file="../0001/index.xml#a1234567"

The ICH eCTD Specification defines the "modified-file" attribute as follows:

modified-file="../0001/m2/27-clin-sum/literature-references.pdf"

On Line 280, it would be better to provide an example for a relative path of a document in Module 2 – 5.

VI. A. 2. Drug Substance Element Attributes
On lines 576 and 583 there is a space between the closing tag character "/" and the element name. These spaces should be deleted.

V. B. 1. Drug Substance Summary Element Attributes
On lines 414 and 419, change substance="Substace-USAN" to substance="Substance-USAN"

VI. A. Module 3 element table
On line 523, change "The attributes and the used of..." to "The attributes and the use of..."

VII. Module 4: Safety
In the table following line 689, there doesn't seem to be tags for the preclinical data and related files.

On line 711, the section title is "Module 5:Efficacy. The Module 5 title in the "Comprehensive Table of Contents Headings and Hierarchy" document uses "Module 5 Efficacy" and the main guidance document uses "Module-5: Clinical Study Reports" (see line 600).

Study Tagging Files Specification

It would be very helpful to have version numbering or dates associated with this document.

FDA should provide the rationale for the STF so industry has a better appreciation of the real purpose.

There needs to be a more detailed explanation of the STF. The concept is rather hastily explained and illustrated, and it is quite confusing. A more detailed and thorough explanation is needed?

Please clarify where the STF is needed (e.g. all clinical and/or nonclinical study reports). This is not readily apparent from the guidance.

The contents of the eCTD backbone and the STF specification are duplicated in some instances (e.g. the title attribute) and some information currently specified for the STF guidance may be better placed in the eCTD backbone.

Metadata are being validated by stylesheets, which could be regional. This could pose problems on two fronts: (1) stylesheets should contain formatting, while content should be the domain of the DTD and (2) pick lists should be managed globally rather than regionally, i.e., by ICH. If this is done regionally, sponsors may have to respond to different approaches.

The element and attribute names within the STF DTD should be changed to promote a clearer understanding of the content. For example, the document-identifier element should be called study-identification and the doc-id element should be called study-id.

The STF Specification is incomplete for all of the needs identified in the Comprehensive Table of Contents Headings and Hierarchy. There seems to be incomplete definition of attributes and elements within the STF DTD or Stylesheet. For example:

- "Dose" for Single Dose Toxicity studies;
- "Duration" for Repeat Dose Toxicity studies; and
- Antiviral and Antibacterial Report components.

In many cases there is flexibility with respect to how the information can be organized within the STF file. While sponsors may like the flexibility of creating these files in different ways, it is most likely that vendors and sponsors would benefit from clarification regarding which way of organizing information within the STF should be supported. For example, content blocks could be used to organize and group related files. Can it be assumed that process/transformation software and/or viewing software will be able to interpret "inheritance" within content blocks? For example, if a content block is given the associated property for a specific "site", is this the equivalent to associating that same site to each individual file? Additionally, if a content block is identified for patient case reports or patient profiles, can a file tag be associated with the parent content block and then not associated with each patient CRF file or each patient profile?

On page 1, the 5th paragraph, please clarify the sentence "The file or collection of files and the STF should be placed in the same directory separate from other independent studies." The sentence stating "A subdirectory structure can be used, but it is not specified here." suggests that the folder structure is optional. This would be in contrast to draft guidance 'Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions (draft 08/18/03)', which recommends separate folders for 'datasets', see Line 590-593 and Line 686-688.

On page 2, lines 6-8 states "In each of these examples the modified-file attribute should have a value that references the path and filename of the old STF XML file". This statement is in conflict with the two examples in the center of the same page labeled serial 0004 and serial 0014. Lines 6-8 are consistent with the ICH eCTD Specification.

Page 4 is blank.

On page 8, the route of administration choices are not adequate and they should be expanded (e.g., intranasal).

On page 8, the value "No-treatment-control" is the only value that contains an upper case character. Please clarify whether these values are case sensitive and if this value should be lower case as the other values.

On page 8, specific attributes to identify microbiology reports are needed.

On the last full paragraph of page 9, the second paragraph of page 13 and the first paragraph of page 14, it is not necessary to specify "For submissions to the US regulatory authority, Food and Drug Administration (FDA),...".

On page 10, additional appendices should be allowed. Other agencies will also need the ability to specify that certain appendices are available upon request.

On page 15, the next to the last sentence of the last paragraph it states "This study will be submitted to both the Japan and US regulatory authorities and contains some additional test results for the Japan regulatory authority." This example would not result in a submission to FDA, but only to Japan.

Several clarifications are needed on the usage of the STF when studies are in multiple categories. For example, there may be cases where studies are associated with multiple categories within a CTD/eCTD. This may occur at any one point in time or may be due to the nature of the study with respect to changes in the indication associated with the dossier. In these cases, should all of the study leafs or files be repeated or can the STF simply be referenced from multiple locations? See the examples below:

- A single study could satisfy multiple categories within the eCTD. This case has been cited for ADME studies. Can a single STF be referenced from multiple leaf locations in the backbone?

- If a study synopsis and CRFs are submitted to support safety for one indication but not seen as directly relevant to the claimed indication, the STF file may be submitted in 5.3.5 under this indication. At a later point in time, the same study, with full report, data sets, patient CRFs, etc. may be submitted as a supplement supporting a new indication. At this point, do all of the supporting leaf files need to be recreated or can a new STF simply be submitted as an amendment to the original one?
- In the case of study information submitted to an IND, does each leaf need to be recreated or can we simply refer the original STF from the Marketing application?
- If a study is being used in multiple marketing applications, how can the individual files be referenced or can the STF alone be referenced?

Again, we appreciate the opportunity to comment on the details of the proposal, and applaud FDA's initiative to implement the eCTD.

Sincerely,